UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,293	02/13/2002	Ekaterina Alexsandrovna Tabolina	US-145O	3493

38108 7590 04/04/2007

CERMAK & KENEALY LLP
ACS LLC
515 EAST BRADDOCK ROAD
SUITE B
ALEXANDRIA, VA 22314

EXAMINER	
GANGLE, BRIAN J	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/073,293	**Applicant(s)** TABOLINA ET AL.	
	Examiner Brian J. Gangle	**Art Unit** 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 March 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *1*.
   Claim(s) rejected: *1-3 and 31-33*.
   Claim(s) withdrawn from consideration: *4-30*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

The amendment filed on 3/15/2007 under 37 CFR 1.116, in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because, minimally, the proposed amendment introduces new limitations that have not been previously considered and would require further search and consideration.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, all pending rejections are maintained for reasons of record and are reiterated below. Those arguments that are applicable will be addressed as they apply to the rejections of record.

Specification Objection Maintained

The objection to the specification because it contains an embedded hyperlink is maintained for the reasons set forth in the previous office action.

Claim Objections Maintained

The objection to claim 1 because of the following informalities: section (B) of the claim reads "1 to 12 amino acids in the amino acid sequence in SEQ ID NO:4, and and wherein said protein" is maintained for the reasons set forth in the previous office action. It is assumed that the second "and" is a typographical error. Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claim 31under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the inclusion of new matter (i.e. the range of 1-5 amino acids), is withdrawn in light of applicant's arguments thereto.

Claim Rejections Maintained

35 USC § 112 – New Matter

The rejection of claims 1-3 and 31-33 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the inclusion of new matter, is maintained for the reasons set forth in the previous office action.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, this rejection is maintained for reasons of record and is reiterated below.

Claim 1 recites the limitation "(B) a protein comprising an amino acid sequence including deletion, substitution, insertion or addition of 1 to 12 amino acids" and "(D) a protein comprising an amino acid sequence including deletion, substitution, insertion or addition of 1 to 11 amino acids." The ranges "1 to 12" and "1 to 11" do not appear in the specification, or original claims as filed. Applicant points to page 15, lines 5-11 in the specification to support these limitations, however, the ranges "1-12" and "1-11" are not supported. Therefore, these limitations are new matter.

35 USC § 112 – Enablement

The rejection of claims 1-3, 31, and 33, under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons set forth in the previous office action.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, this rejection is maintained for reasons of record and is reiterated below. Those arguments that are applicable will be addressed as they apply to the claims of record.

Applicant argues:

1. That the examiner did not address the scope of claim 31, which is limited to variations of 1 to 5 amino acids. Applicant argues that the examiner's rejection is restricted to and is based on the limitation of variations of 1 to 12 amino acids. Applicant suggests that the final action was incomplete and requests withdrawal of finality.

2. That the limitation of variations to 1 to 5 amino acids is a very small variation and that it is within the skill of the art to determine variant proteins which will maintain the required functions. Applicant argues that, as bacteria are simpler than eukaryotic organisms, the examiner's arguments regarding post-translational modification and the effects of amino acid alteration within a protein are not entirely applicable. Applicant suggests that, because bacteria are simple, less experimentation is required to determine protein activity.

3. That the examiner's arguments regarding the extremely large number of possible variants encompassed by the claims do not apply. Applicant suggests that the skilled artisan would not need to make and test each of these variants and that one could use their knowledge of conservative substitutions to increase the chance for retention of activity.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the rejection of record is not based on the limitation of "1 to 12." As stated previously, changing a single amino acid can drastically alter the folding and activity of a protein. Therefore, any changes in the sequence (including changes of 1 to 5 amino acids) are encompassed by the rejection. The examiner's discussion of the limitation of "1 to 12" was in response to applicant's arguments, and the rejection is not based solely on this limitation. Consequently, the final action was a complete action that addressed each of the claims.

Regarding argument 2, as with variations of 1 to 12 amino acids, a change of 1 to 5 amino acids is a phenomenally large and virtually incalculable number. As stated previously, it is within the skill of the art to make and test these possible polypeptides; however, applicant has provided no guidance whatsoever regarding which amino acids could be changed, deleted, or added to achieve or maintain the claimed function. Merely enumerating the possible polypeptides would be undue experimentation. Considering the laboratory processes required to generate and test bacterial mutants, making and testing an incalculable number of variants certainly constitutes undue experimentation. The fact that bacteria are simpler organisms may make them easier to work with than eukaryotes, but this in no way decreases the number of variants that are encompassed by the claims, and the amount of experimentation required would still be extremely large. Further, applicant's suggestion that post-translational modifications are not a factor in bacteria is incorrect. It is well known that bacteria modify proteins after translation. Correctly folded proteins are a requirement for activity in all organisms. Also, it is

incorrect to suggest that single amino acid changes do not alter protein function in bacteria. Point mutations can alter protein function regardless of the simplicity of the organism.

Regarding argument 3, there is no mention in the claims of conservative substitutions. All deletions, substitutions, insertions and additions are encompassed by the claims. In fact, one cannot make a "conservative" deletion, insertion, or addition. Additionally, applicant appears to be suggesting that one could use their skill to determine which changes could be made while maintaining the required function. There is no guidance whatsoever in the specification regarding which changes could be made. In fact, applicant has not actually disclosed what activity the claimed proteins have. With no knowledge of the claimed proteins, other than the sequence, there is no guidance regarding what changes should be made. Finally, as stated previously, changing even a single amino acid (even conservative substitutions) can alter the activity of the protein, even in bacteria.

35 USC § 112 – Second paragraph

The rejection of claims 1-3 and 31-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained for the reasons set forth in the previous office action.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, this rejection is maintained for reasons of record and is reiterated below.

Claim 1 is rendered vague and indefinite by the phrase "increasing the activities of a protein." According to the specification, the function of the claimed proteins is not known. Therefore, it is not clear what "activities" said protein is capable of or whether the protein has more than one activity. If the protein has only one activity, one cannot increase its "activities."

Claim 1 is rendered vague and indefinite by the phrase "or its analogs to the bacterium." It is unclear what the analog is an analog of. Is it the protein, the L-amino acid, or the bacterium that has an analog?

Claim 2 recites the limitation "said DNA" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. The claim mentions a DNA coding for a protein, and a DNA sequence which regulates expression. Which of these is "said DNA"?

Claim 31 is rendered vague and indefinite by the phrase "wherein the number of deletion, substitution, insertion or addition of amino acids in the amino acid sequences in SEQ ID NOS:4 and 6 is 1-5." It is not clear whether this is intended to mean that 1-5 amino acids can be changed, or whether the number of changes (i.e. deletions, substitutions, insertions, or additions) must be from 1-5. Further, applicant has not specified whether the altered proteins are intended to be (B) and (D) from claim 1, or whether (A) and (C) can be altered in this manner.

Claim 32 is rendered vague and indefinite because the claim is dependent upon claim 31, where the proteins of SEQ ID NO:4 and 6 must have been altered. However, proteins with the sequences of SEQ ID NO:4 and 6 that are altered would not be the proteins encoded by SEQ ID NO:3 and 5, as required by claim 32. Further, it appears that, to meet the limitations of claim 31, the bacterium must have (B) and (D) from claim 1. However, claim 32 is drawn to the bacterium with proteins (A) and (C), which the bacterium would not have.

Claim 33 is rendered vague and indefinite because the claim is dependent upon claim 32. As stated above, to meet the limitations of claim 32, the bacterium must contain (A) and (C), but not (B) and (D). However, claim 33 requires (B) and (D). It is not clear how this can be accomplished.

35 USC § 102

The rejection of claims 1-2 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Furukawa *et al.* (US Patent 4,996,147, 1991) is maintained for the reasons set forth in the previous office action.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, this rejection is maintained for reasons of record and is reiterated below.

As outlined previously, Furukawa *et al.* teach a bacterium belonging to the genus *Escherichia* and having resistance to rifampicin, lysine, methionine, aspartic acid and homoserine, and an ability to produce L-threonine until L-threonine is accumulated in the culture

(paragraph bridging cols. 1-2). The bacterium of Furukawa has an enhanced ability to produce L-threonine (col. 3, lines 48-52). The products of the prior art reference appear to be the same or an obvious or analogous variant of the product claimed by the applicant because they appear to possess the same or similar functional characteristics, i.e. a bacterium belonging to the genus *Escherichia* which has enhanced L-amino acid production. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon. Further, the proteins named in the instant application are proteins found naturally in *E. coli*. Thus, in the absence of evidence to the contrary, the bacterium of Furukawa *et al.* has enhanced amino acid production due to an alteration in the expression of regulation sequences of DNA on the chromosome of the bacterium.

The rejection of claims 1-3 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Sano *et al.* (European Patent Application Publication 0 643 135 A1, 1995) is maintained for the reasons set forth in the previous office action.

Since applicant's arguments are predicated on an amendment not of record. Said arguments are deemed non-persuasive. Consequently, this rejection is maintained for reasons of record and is reiterated below.

Applicant has claimed an isolated L-amino acid bacterium from the genus *Escherichia*. Although Sano disclose the same product, they do not disclose that the product is produced by the same method of making (i.e. enhanced activity of SEQ ID NO:4 and 6, obtained by

transformation with a multi-copy vector). However, it should be noted that the instant claims constitute Product-by-Process type claims. In Product-by-Process type claims, the process of producing the product is given no patentable weight since it does not impart novelty to a product when the product is taught by the prior art. See *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983) and *In re Brown*, 173 USPQ 685 (CCPA 1972). Consequently, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught in by the prior art. See *In re King*, 107 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); *In re Merz*, 97 F.2d 599, 601, 38 USPQ 143-145 (CCPA 1938); *In re Bergy*, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979). Finally, since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See *In re Best*. Moreover, as disclosed in the instant specification (page 3, line 11 – page 4, line 7) and in Blattner *et al.* (IDS filed 6/17/2002, document AW), the claimed proteins are found naturally in *E. coli*. Therefore, in the absence of evidence to the contrary, the isolated bacterium with enhanced L-amino acid production disclosed by Sano is the same as the composition of the instant claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle
AU 1645

ROBERT A. ZEMAN
PRIMARY EXAMINER